III. REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based on the following remarks are respectfully requested.

Claim 16 and 25 are amended, claim 17 is canceled, and new claims 28-36 are submitted. Upon entry of the amendment, claims 16 and 23-36 will be pending in the application.

Claim 16 is amended to be directed to a method of killing a B cell lymphoma cell in a subject, comprising administering a therapeutically effective amount of an immunoconjugate to the subject, wherein said immunoconjugate comprises an anti-CD20 antibody or an immunogenic fragment thereof that binds to CD20 expressed by a B cell lymphoma cell in the subject, and wherein the anti-CD20 antibody or immunogenic fragment thereof possesses human effector function, and is fused at its carboxy terminus to interferon-α-2a (IFN-α-2a) that binds a receptor expressed on the surface of an effector cell. Support for identifying the cell targeted by the claimed method as a B cell lymphoma cell is found, for example, in paragraph [0022] on page 8, and in dependent claim 17, which is canceled. Support for describing the claimed method as a method of "killing" B cell lymphoma cells is found in the specification, *e.g.*, in paragraph [0001] on page 1.

Claim 25 is amended by deleting trademark names, by amending the reference to "anti-B1" antibody to refer to "tositumomab" (*see* Macklis, 2000, Int. J. Radiat. Oncol. Biol. Phys., 66(2 Suppl):S30-4, abstract attached), and by amending the reference to "1H4" to refer to "1H4 single chain Fv antibody," *e.g.*, as described on page 3, lines 6-7.

New independent claim 29 is directed to a method of treating B cell lymphoma in a subject comprising administering a therapeutically effective amount of a fusion protein to a subject, wherein said fusion protein comprises an anti-CD20 antibody or an immunogenic fragment thereof that binds to CD20 expressed by a B cell lymphoma in the subject, and wherein the anti-CD20 antibody or immunogenic fragment thereof possesses human effector function and is fused at its carboxy terminus to interferon-α-2a (IFN-α-2a) that binds a receptor for IFN-α-2a that is expressed on the surface of an effector cell. Support for new claim 29 is found in the specification, *e.g.*, in paragraphs [0020]-[0022] on page 8, which describe a method of treating

cancer comprising administering a fusion protein of the invention that targets an anti-CD20 antigen on a B cell lymphoma cell and comprises IFN-α-2a, and in paragraph [0001] on page 1, which describes the binding of the IFN-α-2a of the fusion protein to its receptor on an effector cell to facilitate the killing of the targeted cell.

New claim 30 is directed to the method of claim 29, and identifies the effector cell as being selected from the group consisting of natural killer (NK) cells, lymphocyte-activated killer (LAK) cells, macrophages, monocytes, and polymorphonuclear (PMN) cells, *e.g.*, as described in paragraph [0029] on page 10.

News claims 31-35 are directed to the method of claim 29, and identify the anti-CD20 antibody or immunogenic fragment thereof as, respectively, rituximab, 1F5, ibritumomab, 1H4 single chain Fv antibody, and tositumomab (anti-B1) antibody, *e.g.*, as described in paragraph [0006] on page 3.

New claims 28 and 36 are dependent on claims 16 and 29, respectively, and specify that the immunoconjugate or fusion protein is administered by intravenous injection, *e.g.*, as described on page 23, lines 6-7.

The applicant does not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserves the right to pursue such subject matter in continuing applications.

Patentability Remarks

35 U.S.C. §112, first paragraph

On page 2 of the official action, the examiner has maintained the rejection of claim 25 under 35 U.S.C. §112, first paragraph, because the specification is considered to be enabling for an antibody fragment whose sequence has been published, but not for an antibody for which only the (sequence of) the CDR regions has been published. The examiner appears to be referring to the description in the publication of Haisma et al. (1998) of a single chain Fv anti-CD20 antibody that comprises the heavy and light chain variable region amino acid sequences shown

on page 187 of the reference. The examiner further states that the entire monoclonal antibody as produced by a hybridoma must be described.

The applicant respectfully traverses the rejection. The specification clearly teaches that the claimed invention can be performed successfully using an anti-CD20 antibody or an immunogenic fragment thereof that binds to an antigen expressed by a target cell that is to be eradicated (*see* page 8, lines 3-5). Moreover, the specification defines antibodies or fragments thereof that can be used for the claimed invention as including single chain antibodies (*see* paragraphs [0031]-[0032] on page 10), and expressly identifies the "single chain Fv anti-CD20 mouse mAb 1H4," described by Haisma et al. (Blood, 1998, 92:184-90; reference IIR of the IDS filed June 14, 2004) as an anti-CD20 antibody that can be used for the claimed invention (*see* lines 6-7 of paragraph [0006] on page 3). The publication of Haisma et al., which is incorporated by reference, describes the single chain Fv anti-CD20 antibody 1H4 as comprising the heavy and light chain variable region amino acid sequences shown on page 187 of the reference, joined by a synthetic 15 amino acid $(gly_4ser)_3$ linker (*see* page 186). As described by Haisma et al., the single chain Fv antibody 1H4 binds specifically to CD-20 antigen on the surface of (Daudi) B cell lymphoma cells (*see* page 187). As discussed above, claim 25 is amended to refer to the 1H4 antibody as the "1H4 single chain Fv antibody," in accord with the description of the antibody in the specification and in the publication of Haisma et al. The disclosure of the amino acid sequence of the 1H4 single chain Fv antibody by Haisma et al. enables one of skill in the art to obtain the single chain Fv 1H4 antibody for use in the claimed invention. As discussed in the previous response, the anti-CD20 antibodies specified in claim 25 are readily available to the public, or alternatively are obtainable based on information within the specification. Accordingly, the specification fully enables the invention of amended claim 25. In view of the foregoing remarks and amendment, the applicant respectfully requests that the rejection of claim 25 under 35 U.S.C. §112, first paragraph, for lack of enablement, be withdrawn.

35 U.S.C. §112, second paragraph

On page 5 of the official action, the examiner newly rejected claim 25 under 35 U.S.C. §112, second paragraph, because references to trademark names in the claim are considered to render the meaning of the claim indefinite.

The parenthetical references to trademark names in claim 25 are deleted. Accordingly, withdrawal of the rejection of claim 25 under 35 U.S.C. §112, second paragraph, is respectfully requested.

35 U.S.C. §103(a)

The examiner has maintained the rejection of claims 16, 17, and 23-27, under 35 U.S.C. §103(a) as allegedly being obvious over Davis et al. (2000), in view of Taji et al. (1998).

> To establish a prima facie case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of ordinary skill in the art would (1) provide some suggestion or motivation to modify or combine reference teachings to obtain the claimed invention, (2) teach or suggest all of the claim limitations, and (3) provide a reasonable expectation that the claimed invention can be made or used successfully. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. See In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), also In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) citing In re Raynes, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992), and M.P.E.P. § 2142.

The applicant submits that neither the cited references nor the general knowledge of one of ordinary skill in the art suggested or provided motivation to one of ordinary skill in the art at the time the invention was made to practice the claimed method in which a fusion protein comprising an anti-CD20 antibody fused at its carboxy terminal end to IFN-α-2a is administered to a subject with B cell lymphoma to kill B cell lymphoma cells in the patient.

Davis et al. describes a method for treating B cell lymphoma by separately administering the anti-CD20 antibody rituximab and IFN-α-2a to a patient with B cell lymphoma. Davis et al. teach administering a dose of 5 MIU (million units) of IFN-α-2a by subcutaneous injection three time a week for 12 weeks, and administering a dose of 375 mg/m^2 of rituximab by intravenous infusion once per week on weeks 5-8 of the treatment, for a total of four infusions (*see* page 2646). Davis et al. does not describe or suggest treating a patient with B cell lymphoma by

administering to the patient a fusion protein comprising the anti-CD20 antibody fused at its C terminus to IFN-α-2a.

Taji et al. describes using the anti-CD20 antibody rituximab to inhibit the growth of B cell lymphoma cells *in vitro*, and teaches that induction of apoptosis plays a part in the inhibition of the growth of B cell lymphoma cells by the anti-CD20 antibody. Taji et al. also does not describe or suggest a method comprising administering a fusion protein comprising an anti-CD20 antibody fused at its C terminus to IFN-α-2a to a patient with B cell lymphoma.

Neither Davis et al. nor Taji et al. describe or suggest the claimed method of treating a patient with B cell lymphoma by administering a fusion protein comprising an anti-CD20 antibody fused at its C terminus to IFN-α-2a, to kill B cell lymphoma cells in the patient, as discussed above. However, the examiner alleges that in view of the general knowledge available at the time the invention was made, it would have been obvious for one of ordinary skill in the art to modify the method of Davis et al. by using known methods to make a fusion protein comprising rituximab fused at its C terminus to IFN-α-2a, and to administer the fusion protein instead of separately administering IFN-α-2a and rituximab to the patients as described by Davis et al., in order to reduce the number of painful injections that the patients must receive, and/or to reduce the number of proteins that must be purified in order to treat the patients.

At the time the invention was filed, the general knowledge of one of ordinary skill in the art, in combination with the teachings of the cited Davis et al. and Taji et al. references, would not have suggested or provided motivation to one of ordinary skill in the art at the time the invention was made to practice the claimed method in which a fusion protein comprising an anti-CD20 antibody fused at its carboxy terminal end to IFN-α-2a is administered via intravenous injection to a subject with B cell lymphoma in order to kill B cell lymphoma cells in the patient. For the reasons discussed below, the examiner's allegation that it would have been obvious for one of ordinary skill in the art to modify the method of Davis et al. to obtain the claimed method is incorrect and is unsupported by the medical and scientific literature available at the time the invention was made.

Davis et al. describes a method for treating B cell lymphoma in which IFN-α-2a and the anti-CD20 antibody rituximab are each administered separately using dosages and routes of administration that were accepted by persons of skill in the art at the time as being safe and

effective. Specifically, Davis et al. describes administering a dose of 5 MIU (million units) of IFN-α-2a (Roferon-A, from Roche, Nutley, NJ) by subcutaneous injection to the patient three time a week for 12 weeks, and administering a dose of 375 mg/m^2 of rituximab by intravenous infusion once per week on weeks 5-8 of the treatment, for a total of four infusions (*see* page 2646). The specific activity of the IFN-α-2a used by Davis et al. (Roferon-A) is approximately 270 MIU/mg protein (*see* Roferon-A product information from Roche, copy attached); accordingly, Davis et al. describes a method in which approximately 18.5 micrograms of IFN-α-2a (Roferon-A) was administered subcutaneously to the patient three time a week for 12 weeks. Using the body surface area approximation of 2 m^2 per patient, Davis et al. also describes administering an intravenous dose of 750 mg of rituximab during each of weeks 5-8 of the treatment. Assuming a molecular weight of 150,000 daltons per antibody, each dose of 750 mg of rituximab contains approximately (0.75 grams / 150,000 grams per mole =) 5 micromoles of rituximab antibody. The molecular weight of IFN-α-2a (Roferon-A) is approximately 19,000 daltons (*see* the attached Roferon-A product information). Therefore, a dose of the rituximab/ IFN-α-2a fusion protein containing the amount of rituximab that is accepted as a single dose as taught by Davis et al. (approximately 750 mg) would contain approximately (19,000 g/mole x 5 x 10^{-6} mole =) 0.095 grams, *i.e.*, 95 mg of IFN-α-2a, per injection.

As discussed above, the examiner alleges that it would have been obvious for one of ordinary skill in the art, in view of the general knowledge available at the time the invention was made, to modify the method of Davis et al. by making a fusion protein comprising rituximab fused at its C end to IFN-α-2a, and to administer the fusion protein instead of administering IFN-α-2a and rituximab by separate regimens as described by Davis et al., in order to reduce the number of painful injections that the patients must receive, and/or to reduce the number of proteins that must be purified in order to treat the patients. This argument is fallacious, because modification of the method of Davis et al. to obtain the claimed method in which a rituximab/ IFN-α-2a fusion protein is administered significantly alters the clinical method taught by Davis et al., in which both IFN-α-2a and rituximab are administered by separate regimens that were respectively accepted in the art as being safe and effective (*see* page 2645). If one of skill in the art had contemplated modifying the method of Davis et al. as alleged by the examiner, he would reasonably have considered doing so by administering the rituximab/ IFN-α-2a fusion protein to a patient with B cell lymphoma using a regimen similar or identical to that described by Davis et

al. for rituximab alone, *i.e.*, by administering a dose containing 375 mg/m^2 of rituximab by intravenous infusion once per week for four weeks (*see* page 2646 of Davis et al.). The modified method would therefore replace three weekly subcutaneous injections of 18.5 micrograms of IFN-α-2a given for 12 weeks with four weekly intravenous injections of approximately 95 milligrams of IFN-α-2a. The modified method would alter the time period the patient is exposed to IFN-α-2a from 12 weeks to a significantly shorter period, it would alter the route of administration of IFN-α-2a from subcutaneous injection to intravenous injection, and it would increase the weekly dosage of IFN-α-2a that is administered more than 1600-fold, from approximately 58.5 micrograms to approximately 95 milligrams. Moreover, the rituximab and IFN-α-2a proteins present in a fusion protein would not be expected to show the same pharmacological activities as the separate proteins. As pointed out above, the separate regimens described by Davis et al. for administering IFN-α-2a and rituximab to treat B cell lymphoma were accepted in the art at the time the invention was made as being safe and effective (*see* page 2645). **There is absolutely no precedent or support in the medical literature for the examiner's allegation that the above-described modifications in the safe and effective clinical protocol described by Davis et al. would have been obvious or justified to one of skill in the art at the time the invention was made, in order to reduce the number of injections that the patient receives, and/or to facilitate the purification of the therapeutic proteins.** Moreover, the clinical protocol described by Davis et al. used commercially available therapeutic proteins (Roferon-A® and Rituxan®) that have already been purified by their respective vendors and approved for clinical use. Therefore, contrary to the examiner's allegation, one of ordinary skill in the art would reasonably have considered that the method described by Davis et al. using the commercially available rituximab and IFN-α-2a proteins would entail less work and expense than making and purifying a rituximab/ IFN-α-2a fusion protein.

The examiner continues to incorrectly allege that Davis et al. teach on page 2645 that anti-CD20 antibody such as rituximab and IFN had synergistic effect in preclinical trials (*see* page 4 of the official action). The passage on page 2645 of Davis et al. to which the examiner refers states that "[g]iven the efficacy of rituximab and IFN as single agents and the preclinical results indicating synergistic effects between IFN and anti-idiotypic antibodies, the safety and efficacy of rituximab in combination with IFB-α-2a (Roferon-A) was investigated." Davis et al.

clearly refers to synergistic effects between IFN and anti-idiotypic antibodies, not between IFN and anti-CD20 antibody. Anti-idiotypic antibodies are antibodies that bind to immunoglobulin molecules on the surfaces of B cells. *See* the discussion of synergistic effects between IFN and anti-idiotypic antibodies on page 2645, left column, of Davis et al., and references 23, 23, 32, and 33 cited therein. Moreover, as pointed out in the previous response, Davis et al. report that the therapeutic effect of administering a combination of rituximab and IFN to patient with B cell lymphoma which they observed is no greater than the therapeutic effect reported for administering a rituximab alone (*see* page 2650, left column). **Rather than describing a synergistic effect as alleged by the examiner, Davis et al. do not even report an additive effect of administering IFN-α-2a and rituximab.** Thus, one of skill in the art who wished to reduce the number of injections and the number of potentially harmful drugs given to a patient being treated for B cell lymphoma would regard Davis et al. as teaching away from administering a combination of IFN-α-2a and rituximab, and as teaching instead that administration of rituximab alone may provide the same or greater benefit, with fewer injections, and without unnecessary exposure of the patient to potentially harmful side-effects of IFN-α-2a.

As discussed above, neither the cited references nor the general knowledge available at the time the invention was made described or suggested modifying the method of Davis et al. to obtain the claimed invention. Contrary to the examiner's allegation, one of ordinary skill in the art would not have been motivated by general knowledge available at the time the invention to reduce the number of injections given or the number of proteins purified by modifying the method of Davis et al. by making a rituximab/ IFN-α-2a fusion protein and administering it to a patient with B cell lymphoma instead of separately administered IFN-α-2a and rituximab proteins as taught by Davis et al. Since treatment of a patient with B cell lymphoma by administering a fusion protein comprising rituximab fused at its C terminal end to IFN-α-2a according to the claimed method is a limitation that is neither described nor suggested by the cited references or the general knowledge available at the time the invention was made, the examiner has not made a prima facie case of obviousness under 35 U.S.C. §103(a).

The examiner alleges that one of ordinary skill in the art would have been motivated to make a fusion protein comprising rituximab fused at its C terminal end to IFN-α-2a with a reasonable expectation of success, "since how to make recombinant interferon alpha-2a, and how

to construct anti-CD20 antibody expression construct had been well known in the art before the effective filing date of the instant application." *See* page 4 of the official action. The applicant does not agree that either the prior art and/or the general knowledge available at the time the invention was made would have motivated one of ordinary skill in the art to make a rituximab/ IFN-α-2a fusion protein. Moreover, the examiner has failed to provide any evidence that one of ordinary skill would have considered it to be obvious to modify the method for treating B cell lymphoma described by Davis et al. by administering a rituximab/IFN-α-2a fusion protein according to the claimed method, instead of separately administering IFN-α-2a and rituximab using the accepted therapeutic regimens, with a reasonable expectation of success. As discussed above, modification of the clinical protocol for treating B cell lymphoma described by Davis et al. by administering a rituximab/IFN-α-2a fusion protein instead of separately administering IFN-α-2a and rituximab using the accepted regimens results in significant changes in the time period of exposure and the route of administration of IFN-α-2a, and in extreme changes (*i.e.* greater that 1600-fold increase) in the dosage of IFN-α-2a that is administered. One of ordinary skill would have recognized that the therapeutic effect of the method for treating B cell lymphoma described by Davis et al. depends on the agents that are administered, and on the timing, route, and dosage of their administration. In view of the major changes in these parameters that would result from the modification of the method of Davis et al., one of skill in the art would not have reasonably expected that the modified method would operate successfully.

In view of the foregoing remarks, the applicant submits that a *prima facie* case of obviousness has not been established, and respectfully requests that the rejection of the claims under 35 U.S.C. §103(a) over Davis et al., in view of Taji et al., be withdrawn.

IV. CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

Date: October 19, 2006

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